TREATMENT OF KELOIDS WITH SURGERY AND POST-OPERATIVE BRACHYTHERAPY

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CERTIFICATE

This is to certify that the dissertation titled **"TREATMENT OF KELOIDS WITH SURGERY AND POST-OPERATIVE BRACHYTHERAPY"** of **Dr. A. NEELA CATHRINE** is submitted in partial fulfillment of the requirements for **M.Ch. Branch - III (Plastic Surgery)** Examination of the **Tamil Nadu Dr. M.G.R. Medical University** to be held in August 2006. The period of study was from June 2004 to January 2006.

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DECLARATION

I, **Dr. A. NEELA CATHRINE**, solemnly declare that the dissertation titled "**Treatment of Keloids with Surgery and Post-operative Brachytherapy**" is a bonafide work done by me at Govt. Kilpauk Medical College & Hospital during June 2004 to January 2006, under the guidance and supervision of my Head of Department, **Prof. A. DHANIKACHALAM, M.S., M.Ch., (Plastic Surgery), CTBS (USA)**.

The dissertation is submitted to Tamil Nadu Dr. M.G.R. Medical University, towards partial fulfillment for the award of **M.Ch. Degree (Branch-III) in Plastic Surgery**.

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CONTENTS

INTRODUCTION

"Plastic Surgery is an ocean. One life time is not enough to unravel its deepest secrets."

Perhaps no other problem in Plastic Surgery is so aptly described by this statement as that of the keloid.

Keloids form as a result of abnormal growth of scar tissue usually after trivial injury to the skin. The cause, the inciting factors, its predisposition to occur in certain races, certain injuries and certain sites are still to be explained. Moreover, the phenomenon is peculiar to humans alone.

It is a source of distress to the patient, as even though it is not malignant, it grows to enormous proportions and is not only a cosmetic deformity but also produces itching, burning pain and bleeding.

Treatment is a frustrating experience for surgeons, as keloids have a marked propensity to recur after excision, the recurrence rate being as high as 45% to 100%. Therefore several other modalities of treatment have been tried either alone or in combination with surgery. They include intralesional steroid injections, pressure garments, silicone gel sheet application and various drugs but not with any significant success in rates of control.

Radiotherapy following surgery has been reported as the most effective modality at present with control rates at one year of about 90%. But the traditional problems with radiation therapy have been the field irradiation of surrounding normal areas and the remote chance of secondary cancer.

HDR (High dose radiation) Brachytherapy that allows specific deposition of radiation to tissues, only at the desired site and depth, provided an answer to the above problems. Many studies have quoted very good control rates with no major side effects. It appears that HDR Brachytherapy post surgery could become the ideal management for keloids.

AIM OF THE STUDY

The current study was evolved to test the hypothesis that Surgery followed by HDR Brachytherapy was an effective method of treating keloids.

This study also analysis:

- The age and sex of patients with keloids
- The common sites of occurrence
- The causes for developing keloids
- The clinical signs and symptoms of these patients
- The method of surgery plus radiotherapy employed
- The immediate follow up and condition at one year
- The incidence of complications and recurrence of keloid

SCIENTIFIC FACTS ABOUT KELOID

Background

A keloid is an overgrowth of dense fibrous tissue that usually develops after healing of a skin injury. The tissue extends beyond the borders of the original wound, does not usually regress spontaneously and tends to recur after excision.

The first description of keloids was recorded on Papyrus in 1700 B.C. Subsequently in 1806, Alibert used the term **'cheloide'**, derived from Greek chele, or crab's claw, to describe the lateral growth of tissue into unaffected skin.

Pathophysiology

Hypertrophic (HT) scars and keloids can be described as variations of typical wound healing . In a typical wound, anabolic and catabolic processes achieve equilibrium approximately 6-8 weeks after original injury.

At this stage, the strength of the wound is approximately 30-40% that of healthy skin. As the scar matures, the tensile strength of the scar improves as a result of progressive cross-linking of collagen fibers. At this point, the scar is usually hyperemic and it may be thickened, but it tends to subside gradually over months until a fiat, white, pliable possibly stretched mature scar has developed. When an imbalance occurs between the anabolic and catabolic phases, the scar becomes weak or excessive. Excessive scars are classified either as keloid or a hypertrophic scar.

Scar Comparison Chart

COMPARISON CRITERIA	KELOID SCARS	HYPERTROPHIC SCARS	CONTRACTURES
Most common complexion	Dark	Light	N/A
Extends beyond original wound	Yes	No	Yes
Respond to treatment	Sometimes	Yes	Yes
Raised scarring	Yes	Yes	Yes
Common to burn injuries	No	Yes	Yes

Kischer and Brody declared the **collagen nodule** to be the identifying structural unit of hypertrophic scars and keloids. The nodule, that is absent from mature scars, contains a high density of fibroblasts and unidirectional collagen fibrils in a highly organised and distinct orientation. In addition, keloids and HT scars differ from healthy skin by a rich vasculature, high mesenchymal cell density and thickened epidermal cell layer.

The most consistent histological difference between HT scars and keloids is the presence of broad, dull pink bundles of collagen in keloids, which are not present in HT scars.

Keloids and HT scars are associated generally with HLA-B14, HLA-B21, HLA BW-16, HLA-BW 35, HLA-DR 5, HLA-DQw3 and blood group A. Transmission is reported as both autosomal dominant and autosomal recessive.

8 genes were found to be expressed exclusively in ear-lobe keloid fibroblastic cell lines. Coagulation factor (2) thrombin receptor gene, KIAA 0367 protein gene and matrilin -2 gene were found to be the most commonly expressed genes in keloid cells. Suppressor genes like melanoma differentiation asso-gene-7, Mda-7 (U16261), were expressed in normal skin fibroblasts but were not expressed in keloid fibroblasts and may be implicated in the pathogenesis of keloid lesions.

Reprogramming of gene expression or disordered differentiation from a dermal pattern to that of a chondrocytic / osteogenic lineage, may be involved in etiology of keloid.

Clinical Parameters

Race: Keloids form more frequently in Polynesian and Chinese persons than in Indian and Malaysian persons. As many as 16% of people in a random sampling of black Africans reported having keloids. White and albino persons are least commonly affected.

Sex: The prevalence of keloids has been reported to be higher in young

females than in young males, probably reflecting the greater frequency of ear piercing among females. Keloids and HT scars affect both sexes equally in other age groups.

Age: Onset occurs most commonly in individuals aged 10-30 years. Keloids occur less frequently at extremes of age, although an increasing number of presternal keloids have resulted from coronary artery bypass operations and similar procedures now undertaken in persons of older age groups.

History: Usually the only problem may be cosmetic disfigurement, but HT scars and keloids may become tender, painful, pruritic or infected and they may cause a burning sensation. Sometimes they may cause contractures which may result in loss of function if over a joint.

Physical characters: Keloids manifest as exaggerated growths of scar tissue, usually in areas of previous trauma. They extend past the areas of trauma, projecting above the level of surrounding skin but rarely extend into underlying subcutaneous tissue.

HT scars remain limited to the traumatised area and regress spontaneously within 12-18 months, although regression may not necessarily be complete.

- Keloids range in consistency from soft and doughy to rubbery and hard. Early lesions are often erythematous. Lesions become brownish red and

then pale as they age. Usually are devoid of hair follicles and other functioning adnexal glands.

- Most keloids grow for weeks to months, others grow for years. Growth is usually slow, but some enlarge rapidly, tripling in size within months. Once they stop growing, they usually remain stable or involute slightly.

- Keloids on the ears, neck and abdomen tend to be pedunculated. Keloids on the central chest and extremities are usually raised with a flat surface, and the base is often wider than the top.

- Most keloids are round, oval or oblong with regular margins, however some have claw like configurations with irregular borders.

- Most patients present with 1 or 2 keloids, however a few patients with spontaneous keloids, or those who developed it as a consequence of acne or chickenpox have multiple lesions.

Sites:

- In white persons, keloids tend to present, in decreasing order of frequency on the face (with cheek and earlobes predominating), upper extremities, chest, presternal area, neck, back, lower extremities, breast and abdomen.

- In black persons, the descending order of frequency tends to be earlobes,

face, neck, lower extremities, breast, chest, back and abdomen.

- In Asian persons, the descending order of frequency is earlobes, upper extremities, neck, breast and chest.

Lab Studies: Diagnosis is usually based on clinical findings. Biopsy helps confirm the diagnosis in cases of uncertainty.

Histological Findings: Collagen fibers in granulation tissue are arranged in a whorled pattern, the nodules grow and eventually show thick, compacted, hyalinized bands of collagen lying in a concentric arrangement.

In keloids, this condensation persists indefinitely. While in HT scars, the fibers gradually thin and straighten, so the orientation of collagen bundles appear parallel to the surface of the skin.

TREATMENT

Medical care: No single therapeutic modality is best for all keloids. The location, size and depth of the lesion, the age of the patient and past response to treatment determine the type of therapy used. Prevention is the key, but there are no specific causes that are attributable to its occurrence.

Therapeutic treatment of hypertrophic scars and keloids includes occlusive dressings, compression therapy, intralesional corticosteroid, cryosurgery, excision, radiation therapy, laser therapy, interferon therapy,

imiquimod 5% cream, and other promising but lesser known therapies directed at collagen synthesis.

Prevention: This is the first rule in keloid therapy.

- Avoid performing non-essential cosmetic surgery in patients known to form keloids; However do not consider patients who have only earlobe lesions to be among those who form keloids.
- Close all surgical wounds with minimal tension.
- Incisions should not cross joint spaces.
- Avoid mid-chest incisions; ensure that incisions follow skin creases whenever possible.
- Ensure perfect hemostasis before closure.
- Do not allow healing by secondary intention
- Prevent infection.

Standard Treatments:

Occlusive dressings: Includes silicone gel sheets and dressings, non-silicone occlusive sheets, Cordran tape and Scarguard. Anti keloidal effects appear to result from a combination of occlusion and hydration, rather than from an effect of the silicone.

- Silicone occlusive sheeting with pressure when worn 24 hours a day for 12 months, 34% of patients showed excellent improvement, 37.5% showed moderate improvement and 28% demonstrated no or slight improvement.

- Of patients treated with semi-permeable, semi-occlusive non-silicone-based dressings for 8 weeks, 60% experienced flattening of keloids, 71% had reduced pain, 78% had reduced tenderness, 80% reduced pruritis, 87.5% reduced erythema and 90% were satisfied with treatment.

- **Cordran tape** is a clear surgical tape that contains flurandrenolide, a steroid that is uniformly distributed over each square centimeter of the tape, and has been shown to soften keloids over time. Scar guard is a topical medication containing silicone, hydrocortisone and Vitamin E. This stimulates the release of inactive collagenase precursors that may inhibit new scars forming and reduce existing scars. In a pilot study of 12 patients, Scarguard was applied twice daily, after the removal of a mole, and nothing was applied on a control mole scar. After 2 months, 9 of 12 patients reported that the treated scar was less red and less noticeable compared with the untreated scar.

- In a major meta-analysis of 13 trials involving 559 people, the authors reported that there was great bias in reporting that silicone sheets prevented or were effective in controlling HT scars and keloids and

cautioned that a great deal of uncertainty prevails.

Compression therapy: Involves pressure which has long been known to have thinning effects on skin. Reduction in the cohesiveness of collagen fibers in pressure-treated HT scars has been demonstrated by electron microscopy.

- Compression treatments include button compression, pressure earrings, ACE bandages, elastic adhesive bandages, compression wraps, Lycra bandages and support bandages. In one study, button compression of the earlobe prevented recurrence during 8 months to 4 years of follow-up observation.

- Other pressure-gradient garments are made of light weight porous Dacron, Spandex (also known as elastane) or bobbinet fabric (usually worn 12 - 24 hours a day) and Zinc 0xide adhesive plaster. Overall, 60% of patients treated with these devices showed 75 - 100% improvement.

- A major problem in patients surviving thermal injury is the development of hypertrophic burn scars. A study was performed to determine the factors associated with an increased risk of the development of hypertrophic burn scars. Fifty-nine children (mean age, 3 years; mean TBSA, 14%) and 41 adults (mean age, 37; mean TBSA, 21%) followed from 9 to 18 months formed the study group. The location as well as the time required for the burns to heal were recorded in addition to the age and race of the patients. Sixtythree (26%)

of the 245 burn areas, in these 100 patients, became hypertrophic. No correlation between patient age and the development of wound problems was found. Blacks had more wound problems than others, if the burn wound took longer than 10 to 14 days to heal. The most important indicator of whether wound problems would occur was the time required for the burn to heal. If the burn wound healed between 14 and 21 days then one third of the anatomic sites became hypertrophic; if the burn wound healed after 21 days then 78% of the burn sites developed hypertrophic scars. Based on these findings, the authors developed a protocol to prescribe pressure garments selectively to those areas that would hypertrophy.

Corticosteroids: Intralesional corticosteroid injections have been the mainstay of treatment. Steroids reduce excessive scarring by reducing collagen synthesis, altering glycosaminoglycans synthesis, reducing production of inflammatory mediators and fibroblast proliferation during wound healing. The most commonly used corticosteroid is triamcinolone acetonide (TAC) in concentrations of 10 to 40 mg / ml, administered intralesionally with a 25 - 27 G needle at 4 - 6 week intervals.

- Intralesional steroid therapy either singly or as an adjunct to excision has showed response rates of 50 - 100%, with recurrence rates of 9 - 50% in completely resolved scars.

- Complications of repeated corticosteroid injections include atrophy,

telangiectasia formation and pigmentary alteration.

Recent innovations:

1. Interferon: Interferon α, Interferon β and Interferon γ have been demonstrated in in-vitro studies to reduce keloidal fibroblast production of Collagen I, III and VI mRNA. Interferon α and Interferon β also reduce production of glycosaminoglycans (GAG) that forms the scaffolding for deposition of dermal collagen. Interferon α,β and γ also increase collagenase activity by modulating a p53 apoptotic pathway. p53 is a potent suppressor of interleukin (IL)-6, a cytokine implicated in hyperproliferative and fibrotic conditions.

Interferon injected into the suture line of keloid excision sites may be prophylactic for reducing recurrences. Berman and Flores reported statistically significant fewer keloid recurrences in a study of 124 keloid lesions after post-operative interferon - α2b injection treatment (5 million units, 1 million unit injected per cm of scar) into keloid excision sites (18%) versus excision alone (51.1%) and TAC treatment (58.4%).

2. Verapamil: is a calcium channel blocker that blocks the synthesis / secretion of extra cellular matrix molecules (eg. Collagen,GAGS, fibronectin) and increases fibrinase. In a study of 22 patients with keloids, patients were treated with surgical excision and 5 treatments of Verapamil at 2.5 mg / ml (doses varied from 0.5 to 5 ml depending on the size of the keloid) over a 2 month period and were evaluated at 2 year follow-up. Two patients had keloids that decreased in size, from the original lesion, 2

patients had hypertrophic scars, 4 patients had pruritis, and one patient had a keloid on the donor site.

3. Bleomycin: injections cause necrosis of keratinocytes with a mixed inflammatory infiltrate. In a study, Bleomycin was given at a concentration of 1.5 I.U. / ml to 13 patients using the multiple puncture technique. 7 patients had complete flattening, 5 patients had highly significant flattening, and one patient had significant flattening. In another study on 31 patients treated with 3-5 infiltrates of Bleomycin within a 1 month period, total regression occured in 84% of keloids.

4. 5FU: a pyramidine analog, inhibits fibroblastic proliferation. In one RCT (randomised, controlled trial), 28 patients were treated with weekly injections of 05. - 2 ml at a 50 mg / ml concentration of 5FU for 12 weeks. At 24 week follow up, 70% of patients had more than 50% improvement in keloid size.

In another retrospective study of 1000 patients with HT scars and keloids over a 9 year period, the most effective regimen was found to be 0.1 ml of TAC (10 mg / ml) and 0.9 ml of 5FU (50 mg/ml) upto 3 times a week.

5. Retinoic acid: decreases normal tonofilament and keratohyalin synthesis, increases production of mucoid substances and epidermal growth rate and inhibits DNA synthesis in vitro. In a clinical trial involving 21 patients with

28 keloids and HT scars topical retionic acid was applied for at least 3 months twice daily and showed favourable results in 77 - 79% of lesions. There was a decrease in the size and symptoms of the scar.

6. Imiquimod : Used as a 5% cream induces TNF, interferon α and γ,IL1,IL6,IL8 and IL2.It alters the expression of markers for apoptosis. In one study, 13 keloids were treated with excision in combination with nightly applications of imiquimod for 8 weeks. Ten patients with 11 keloids completed the 6 month study and no keloids recurred after 6 months. Mild irritation and hyper pigmentation were the side effects experienced.

7. Tacrolimus:- is an immunomodulator that inhibits TNF-α and gli-1 an oncogene that has been found over expressed in fibroblasts of keloids. Rapamylin, a close analogue of tacrolimus was found to inhibit gli-1 oncogene in vitro. In a pilot study, 11 patients used tacrolimus 0.1% ointment twice daily for 12 weeks on their keloids. Although the results were not statistically significant, the study showed a decrease in induration, tenderness, erythema and pruritis for most patients.

Radiotherapy

Radiotherapy has been used for the treatment of keloids from 1906.Initially deep X-Ray therapy was used followed by Cobalt irradiation.

Thereafter all the various modes of radiation like α, β and gamma irradiation were used. These were hampered by poor patient compliance due to the local side effects of radiation like eczema, fear of radiation injury to normal tissues and the high costs involved in treating a benign condition. Then came the era of Brachytherapy with surface applicators and intracavitary rods. This has found wide favour and is routinely used now.

- In one retrospective study of superficial X-ray therapy of 24 excised keloids, the author reported a recurrence rate of 53%. Use of iridium 192 interstitial radiation after excisional surgery resulted in a 2 1% recurrence rate after one year. Excisional surgery and pre-operative hyaluronidase solution (150U/ml NaCl) followed by external radiation (7.2 - 10.8 Gy) had a 0% recurrence rate. Adjunctive high dose brachytherapy (Ir 192) used after excision and closure resulted in a 12% recurrence rate after 26 months.

- When excisional surgery is followed by postoperative radiation therapy, the total fractionated dose should be minimum of **12 Gy,** according to a comparative study showing a higher recurrence rate for patients treated with total doses less than 12 Gy.

Surgical care

Cryotherapy

- Cryosurgical media (eg. liq.nitrogen) affects the micro vasculature and causes cell damage via intracellular crystals leading to tissue anoxia.

- Generally 1, 2 or 3 freeze- thaw cycles lasting 10 - 30 seconds each are used for the desired effect. Treatment may need to be repeated every 20 - 30 days. Cryotherapy may cause pain and hypopigmentation in certain patients.

- As a single modality, crysurgery led to total resolution with no recurrences in 51 - 74% of patients after 30 months of follow-up observation.

Excision

Certain techniques have been proposed to reduce the incidence of keloid in sutured wounds.

- Apply basic soft tissue handling techniques at primary wound repair sites.

- Carefully plan closure with minimal tension, paralleling the relaxed skin tension lines.

- Use buried sutures when necessary for layered closure and to reduce tension.

- Apply pressure dressings during immediate post- operative period to

wounds of patients in whom HT scars and keloid formation occur.

- Excisional surgery of keloids alone has been shown to yield a 45 - 100% recurrence rate, and should very rarely be used as a solitary modality. Combination therapy with radiation, interferon and corticosteroids have reduced recurrence rates.

Laser therapy

- Ablation of keloids and HT scars using a CO_2 laser (10,600 nm) can cut and cauterize the lesion, creating a dry surgical environment with minimal tissue trauma. When used as a single modality, the CO_2 laser was associated with recurrence rates of 39 - 92% and when combined with post operative steroids, it was associated with 25 - 74% recurrence rates.

- The Argon laser (488 nm) similar to the C02 laser can induce collagen shrinkage via generation of excessive localised heat. The argon laser has demonstrated recurrence rates of 45 - 93%.

- The pulsed dye laser (585 nm) provides photothermolysis, resulting in microvascular thrombosis. Beginning in 1980s, authors noted that scars become less eythematous, more pliable and less hypertrophic after treatment with 585 nm pulsed dye laser. This remains the laser treatment of choice for HT scars due to its safety, efficacy and relatively low cost.

- The Nd-YAG laser (106 nm) has demonstrated recurrence rates of 53 – 100%.

Other potential therapies

Agents that affect collagen and GAG synthesis like proline - cis - hydroxyproline and azetidine carboxylic acid, tranilast (antiallergic drug) and pentoxifyline (inhibits DNA replication) have been research tools.

Wounds treated with anti-transforming growth factor (decorin) heal with minimal scar tissue formation without affecting wound tensile strength.

Further outpatient care

- Because of the high rate of recurrence, a follow up period of one year is necessary to evaluate effectiveness of therapy

- Advise patients to avoid sharp trauma to skin.

- Minimize inflammation resulting from acne or surgery.

REVIEW OF LITERATURE

Radiotherapy as a single modality or in combination with surgery has been used to treat keloids from as early as 1906.

It has been given in various ways: X-ray (energy = or less than 100 KV) therapy, Teletherapy with photon irradiation or electron (5 MeV or less) and Brachytherapy eg.192 Iridium wires.

- The **biologically effective dose (BED)** is a relatively high dose that must be applied in a short overall treatment time. A BED value of 30 GY was reported as optimal, the treatment administered within 2 days after surgery. Doses less than 10 GY were not effective.

- In 83 keloids on 66 patients treated with 4 x 5 GY (Strontium - 90 surface applicator), 61% patients were extremely satisfied with therapeutic outcome and 51% were extremely satisfied with the cosmetic outcome. The relief from former keloid-caused symptoms, the ear as keloid localisation and male gender were significantly associated with higher satisfaction. The recurrence rate as well as the extent of radiation side effects had no significant influence on patients' assessment.

- 139 patients with 166 keloids treated from 1962 to 1996 were evaluated. Within 48 hours of surgery, they were treated with brachytherapy using

Strontium 90 applicator. Median dose to subcutis was 14 GY (7.5 to 28.5 Gy). Overall recurrence free response rate was 80%. Recurrence was lowest (2%) with keloids of face and neck and highest with keloids over thorax (49%), Keloids following burns had a poorer success rate than those developing after surgery or mechanical trauma ($p<0.001$). There was no difference in outcome related to gender, age or size. No secondary malignancy was reported in 12 years followup.

- 169 patients were treated with HDR brachytherapy between December 1991 and December 1998. 134 were females and facial keloids were a maximum. Within 60 min. of surgery, HDR Brachytherapy in a total dose of 12 GY was administered in 4 fractions of 300 cGY in 24 hours. After a follow up of 7 years, 5 patients had keloid recurrence. Cosmetic results were considered to be good or excellent in 130 / 147 patients. Skin pigmentation was observed in 10 patients, telangiectasias in 12 patients. No late effects of skin atrophy or fibrosis were observed.

- HDR Brachytherapy was preferred to X-rays or low energy electron beams as HDR provides a better selective deposit of radiation in tissues and lower degree of normal tissue radiation. Other advantage of HDR brachytherapy over low dose rate brachytherapy are its low cost and the fact that it can be performed as an out patient basis. Gives a good local

control rate without significant sequelae or complications.

- Leibel and Phillips used dose regimens of 9 - 16 GY in 3 to 4 GY fractions. Excellent cosmetic results have been reported in 95% of cases, and relapse rates range from 2 % to 27%. Perez describes doses of 10 - 15 GY given in 2 - 3 fractions.

- Berman B. Bieley used 10 GY in 1 fraction or 12 to 16 GY in 3 to 4 fractions (400 ccy x 3 to 4 fractions) and has obtained good results. The authors concluded that radiation therapy using various protocols, has been a safe and efficacious modality in reducing recurrence.

- In another study, 36 patients underwent earlobe keloid excision followed by 1800 cGY of radiation therapy in three equally divided doses over 5 to 7 days. In a follow-up of 5 - 6 years, there was only one recurrence (2.8%). One patient developed radiation dermatitis followed by patchy hypopigmentation.

- Beta radiation alone was found to be effective in the eradication of symptoms (55% relief), while results in the reduction of size of lesions have been poor (11%). Surgery combined with postoperative beta radiation therapy yielded a 67% success rate. The success rate was 75% when radiation was delivered within 48 hours of surgery. Preoperative radiation was found to be of no

advantage.

- 203 Keloids were excised and postoperative kilovoltage irradiation was given to prevent regrowth, in Iowa University hospitals. A minimum of one year follow up was advised to evaluate results. Likelihood of failure was too great to justify routine use of less than 900 cGY. A dose greater than or equal to 1500 cGY was sufficient to control 90% of them without re-excision.

- Another study compared the efficacy of ortho-voltage and electron beam radiation. 126 keloids were treated with surgery followed by radiotherapy and after a median follow up of 12 years it was concluded that higher post treatment recurrence were noted with keloids forming at infected sites and in patients with family history. No increased likelihood of recurrence was noted with respect to patient age, sex or ethnicity, keloid size or location, individual keloid history, or prior therapy or radiation type used. The results showed that radiation therapy is a useful and effective method of keloid eradication and electron beam radiation offers no advantage over orthovoltage radiation.

- 75 patients with 113 keloids, 74% involving the ear lobes was treated with superficial X-ray therapy with a most frequent dose schedule of 12 GY in 3 fractions over 3 days. Control rate was 73%. Keloids greater than 2 cm, those that had previous therapy, and those occurring in men

were found to indicate a high likelihood of recurrence. The mean time to recurrence was 12.8 months. There was no complication from this low dose treatment.

- A German study used an automatic water phantom to evaluate the dose distribution in tissue. Further more, a series of measurements were done on patients using thermoluminescence dosimeters (TLD) to estimate the doses absorbed by the organs at risk. 134 keloids were treated with electron beam irradiation following surgical excision. A high control rate of 84% with minimal side effects was observed. Electron radiation provides better dose distribution in tissue and therefore less radiation burden to organs at risk. After a mean follow up of 7.2 years, no severe side effects or malignancies were observed.

- A study from Japan between the years 1988 and 1994 treated 110 patients with 139 keloids with surgery and post operative irradiation with a 4 MeV electron beam, 1-3 days after surgery, for three consecutive days. The total doses were 15 GY or 18 GY. Control rates for keloids and hypertrophic scars were 76% (57 / 75) and 93.8% (60 / 64) and overall effectiveness was 84.2%. No remarkable side effects or malignancy was observed. So they have dispensed with low energy X-ray machines as electron beam delivers peak dose at the site of keloid and the depth of penetration is limited.

- In 1989 Sallstrom published his results on treating 124 patients with keloids with surgery and post operative X-ray radiation, begun within 24 hours of surgery. Patients with a two year history of keloid were included and good or excellent results were observed in 24 months followup in 92%. Slight hyperpigmentation was found in 31% and telangiectasis in 15%.

- A prospective randomised trial comparing the efficacy of corticosteroid injection and radiotherapy after excision of 31 keloids, showed that 2 of 16 keloids (12.5%) recurred after radiotherapy, while 4 of 12 (33%) recurred after intra lesional steroid. Radiotherapy was found to be more effective in preventing recurrence.

- 11 sternal keloids in patients 14 to 16 years of age were treated with surgery, skin grafting and radiation therapy. RT was given to suture lines only using 3 doses of 500 cGY each, within 7 to 14 days of surgery. Follow up ranged from 1 to 24 years. Only one patient demonstrated recurrence. Six patients received post-operative episodic steroid injection for itching or nodule formation without a recurrence.

- The data of 139 patients with 166 keloids between 1962 and 1999 was evaluated for prognostic factors and outcomes. Treatment commenced within 48 hours after surgery. Radiotherapy was given as brachytherapy using an integrated radionuclide 90Sr- 90Y surface applicator. The

median dose delivered subcutis was 14 GY (7.5 to 28.5GY). The overall recurrence free response was 80%. Response rates differed significantly ($p<0.001$). The recurrence was lowest with keloids of face and neck (2%) and highest with keloids of thorax (49%). Keloids following burns had a poorer success rate than those developing after surgery or mechanical trauma ($p<0.001$). There was no difference in outcome related to gender, age or size.

- In another similar study from Japan, 378 cases of keloids were surgically removed and patients treated with 15 GY electron beam irradiation and followed for 18 months. Recurrence occurred in 2 sites on 14 earlobes (14.3),in 2 sites on 12 necks (16.7%), 22 of 51 anterior chest wall (43.1%), in 13 sites in 33 scapular regions (39.4%), in four sites on 15 upper limbs (26.7%), in 4 sites in 11 suprapubic regions (36.4%) and one site in 11 lower limbs (9.1%). The overall recurrence was 32.7%. High stretch tension regions of chest, scapula and suprapubic regions showed a higher recurrence that the authors suggested to be treated with escalating doses of radiation therapy.

- In a landmark study by Raj Ragoowansi et al, 80 keloid scars were treated (59% female and 76% non-white) and 44 percent were located on earlobes. For all patients prior treatment without radiotherapy had failed.

In this study extralesional excision was followed with immediate external beam radiotherapy. A 10 GY dose of superficial 60 kV or 100 kV photon irradiation was given within 24 hours of the operation. The main outcome measure was freedom from recurrence of keloid scars. Results were that all keloid scars were controlled at 4 weeks. Probability of relapse at one year was 9 percent and at 5 years was 16 percent. The earlobe showed no greater chance of relapse than other sites on the body.

- In reviewing the text of published articles and in MEDLINE searches for radiation induced cancers, only five cases of possible radiation induced cancers after keloid treatment have been documented. Radiotherapy has been used frequently and one series has followed patients for up to 20 years and found no cancer induction. One case of thyroid carcinoma occurring in a potential exit dose site was reported 8 years after the treatment of a keloid on the chin of an 11 year old child, but subsequent investigations raise some doubts about causation.

A second case involves bilateral breast cancer developing 29 years after radiotherapy for chest wall keloid treatment given at 26 years of age. In a third case, a basal cell carcinoma developed 10 years after radiotherapy. A fourth case is of a parathyroid adenoma occurring 38 years after RT to the neck for keloids when the patient was 10 years old. A fifth case is of a 36 year old woman who had a localised fibrous

mesothelioma of the pleura and an ipsilateral breast carcinoma 23 years after receiving external radiation therapy at 13 years in the treatment of a chest wall keloid.

From literature review, there is documentation that about 6741 keloids have been treated with radiotherapy. With these 5 cases, the crude risk of developing cancer after radiotherapy is 5:6741 or 1:1348. Cancer is diagnosed each year in 1 in every 250 men and 1 in every 300 women. It is difficult therefore to assign risk of radiotherapy without a defined population of exposed cases and matched controls to compare and without a long-term follow-up.

PATIENTS & METHODS

This study was carried out in the Departments of Plastic and Reconstructive Surgery, Kilpauk Medical College and Government Royapettah Hospital and in the Department of Radiation Oncology, Government General Hospital and Dr. Rai Memorial Hospital.

The period of study was from June 2004 to January 2006.

Patients seeking treatment for keloids and attending the Out Patient Departments of Plastic Surgery were candidates for the study. Most patients had keloids that were at high risk for relapse because they had been previously excised and had recurred. The patients were chosen at random and the study group consisted of 15 patients. Keloidal scars of any duration, any etiology and any site were enrolled into the study. The only patients excluded were children below twelve years of age.

A patient proforma was filled up detailing the history (duration, site, etiology, symptoms, previous treatment history and family history); the clinical features (site, size, surrounding skin, similar lesions elsewhere, ulcers, infection, appearance and quality of skin).

An informed consent was obtained from the patient. The treatment plan, the advantages and problems of the procedure, the necessity of stringent follow-up were explained. The other treatment options available

were also highlighted.

The keloid was then excised extralesionally except in a few large earlobe / helical keloids where intralesional excision preserved available normal skin, under local or general anaesthesia as the case required. The wound was closed primarily without tension in one or two layers of non-absorbable simple sutures, after securing complete hemostasis.

The patient was given HDR Brachytherapy starting on the first postoperative day. A mould of the operated site was prepared with two layers of dental compound and 2 micro catheters were sandwiched within it and strapped to it at a distance of 1 cm from each other. The mould was then fixed to the operated scar, the catheters at 5 mm on either side of the scar. These catheters were then attached to the HDR brachytherapy unit and Iridium 192 seeds were passed through it to reach the target i.e. the suture line.

4 fractions of 500 cGY, a total of 2000 cGY were given, with a minimum of 6 hours gap between fractions and the treatment was completed within 72 hours of Surgery.

In some patients, radiotherapy was given with a linear accelerator delivering 1500 - 2000 rads to the suture line using a 6 MeV machine that delivered approximately 2000 rads to the sub cutis. The

source was kept in contact with the operated site, the beam was centered on the scar and all surrounding tissue was shielded with lead bars. This was given within 24 hours of surgery.

In both cases, the applied dose point was 100% at the Dmax, which was at the skin surface for this superficial therapy. The 90 percent isodose target area was the operated scar. The maximum depth of penetration of radiation was 0.5 cm in HDR brachytherapy and 1 cm in a linear accelerator. This was achieved by using biological tissue equivalents. In the cases where both anterior and posterior sides had to be irradiated, for example in the earlobes, the depth of penetration was kept at 2cm.

Clinical photographs were taken

- pre-operatively
- during brachytherapy
- at suture removal and
- during follow-up visits.

Sutures were removed on the 7th to the10th postoperative day. All patients were routinely advised to wear compression garments.

Patients were followed up

- Weekly for the first two weeks or until suture removal
- Once a month for 3 months
- Every 2 months for 1 year.

During each visit note was made of

- Scar widening or hypertrophy
- Any local side effects
- Systemic complaints
- Recurrence at site of surgery

Recurrence was defined as the clinical evidence of a nodule or obvious return of lesion.

End point of study: Combined modality treatment - Surgery with HDR Brachytherapy, was concluded to be effective if no recurrence of the lesion was detected at **One** year.

OBSERVATION

- 15 patients in this study included 13 women and 2 men making a male: female ratio of 1 : 6.5.

- The age range of the patients:

Age	**13 - 20 yrs**	**21 - 30 yrs**	**31 - 40 yrs**	**>40 yrs**
Number	5	5	4	1

- The duration of the keloids in these patients ranged between 6 months to 18 years.

- The **ear** was the most common site of involvement seen in 11 out of 15 cases. In five cases, the helix (site of secondary ear boring) and in 6 cases the ear lobe had keloids.

- In 5 cases, both the anterior and posterior surfaces of the ear were involved.

- 4 patients had bilateral involvement. In such cases, both sides were operated but only one side was irradiated. The other side therefore acts as a control.

- The sites that were found in this series are :

Ear	-	11
Chest	-	1
Neck	-	1
Shoulder	-	1
Face	-	1

- Trauma and infection were found to be the most common inciting factors. Trauma ranged from minor injury due to nail scratch to significant trauma like a cut with a sunmica sheet or surgery.

- The initiating causes are as described:

S.No.	Causes	Number
1.	Earboring	4
2.	Infection Complicating Earboring	3
3.	Major Trauma	3
4.	Nail Scratch	2
5.	Incision & Drainage of Abscess	2
6.	Ear Lobe Repair	1

- All patients requested treatment because of the unsightly nature of the keloid. 6 patients also complained of occasional itching and 4 patients of a dull pain exacerbated by accidental trauma to the lesion.

Bias in the Study :

- There has been an unconscious bias in recruiting cases that have been recalcitrant to previous treatments, as 11 out of 15 cases have had surgical excision of the lesion before and has since recurred. 3 cases had been operated twice and one case thrice before.

- Similarly 8 of 15 cases have had courses of steroid injections, 3 patients had been injected twice and one patient had 20 injections over 3 courses.

- The list of previous treatments that had been done for keloids in this series were:

Treatment	Number %
No prior treatment	3 (20%)
Surgery	11 (73%)
Steroids	8 (53%)
Ointments	2 (13%)
Silicone gel	1 (6.6%)
Others (homeopathy, acupuncture)	1 (6.6%)

The size of the lesions was again a wide range, starting from 5 mm x 5 mm in an ear lobe keloid to 9 x 3 cm keloid on the anterior chest.

Size	5 mm. to 2 cm.	3 cm. to 5 cm.	> 5 cm.
Number	7	4	4

Keloids that blanched on pressure and appeared erythematous were found in 2, whereas the rest were firm to hard mature lesions. One lesion on the face that had been operated thrice earlier had both mature and erythematous areas.

With regards to skin texture, in this series there was no difference in the occurrence of keloids in fair, brownish or dark skinned people, but oily and thin-skinned people were more in number (11 : 4).

HDR Brachytherapy was given in 9 patients and the linear accelerator was used in 6.The patients had no major problems during the administration of radiotherapy but for some tenderness due to the handling of the operated scar.

The clinical picture during follow-up is depicted in the tabular column:

Follow-up

Time	Pain	Itching	Nodule	Recurrence
2 weeks	No	No	No	No

4 weeks	No	No	No	No
6 months	1	2	1	No
1 year	No	1	No	1

- The keloid scar irradiated on the upper chest developed a nodule in 6 months and recurred as a hypertrophic scar at 1 year. The patient has been advised salvage therapy with silicone gel sheet and compression garment.

- 1 patient complained of pain at 6 months, a small stitch granuloma was observed, that subsided with removal of remnant suture and antibiotics.

- 2 patients complained of itching at 6 months and were treated with antihistamines, but the scars were supple with no evidence of recurrence.

In this series, only one case has registered a treatment failure [1 in 15] giving a ***recurrence rate of 6.66%***

The control of ear lobe keloids has been **100%** at one year.

The complications encountered during therapy were all minor and transient.

- 2 patients developed hyper pigmentation that settled in 6 months.

- 3 patients had an immediate erythema after radiotherapy that subsided in 2 weeks.

- One patient whose keloid in the neck was irradiated developed an ipsilateral facial oedema on the first post-radiotherapy day, that disappeared in 2 days.

- A 45-year-old lady, whose large helical keloid was excised, developed a wound gape at suture removal that healed without a hypertrophy in a week's time.

DISCUSSION

This study reinforces certain facts about keloids.

Sex: There is a higher prevalence of keloids in young females. Studies have quoted figures of 60% *(Raj Ragoowansi et al)* and 80% *(Guix et al)* of patients being female. In this study too the male: female ratio is 1:6.5, the increased incidence mainly because of the common practise of ear boring in females.

Age: Keloids affects young people between 10 - 30 years. In most studies in the literature the mean age is between 25 to 30 years. The mean age of this study group is 27 years. As it afflicts the young, it is even more important to provide a lasting solution to this problem.

Site: The common sites reported in the literature are:

Berman et al	**Guix et al**	**Borgognoni et al**	***This study***
Earlobes	Face	Ear	Ear
Upper Extremities	Trunk	Trunk	Trunk
Neck	Extremities	Upper limb	Face
Breast			Neck
Chest			

Etiology: Keloids are known to occur with relatively minor trauma in contrast to hypertrophic scars. Spontaneous occurrence has been reported in certain genetically predisposed individuals. Wounds that cross skin tension lines, thick skin or in locations like the earlobe, pre-sternal and deltoid regions are more susceptible to abnormal healing.

Earboring alone or the bored site becoming infected was the cause in 50% of this series.

The enigma of the pathology of keloid was illustrated in the case of a lady with recurrent keloid on the chin, who had normal, supple submandibular and neck scars. The same patient also had a very strong familial disposition - her grandmother, father and son have keloidal tendencies.

Symptoms: In most series, cosmetic disfigurement remains the main reason for seeking treatment, as in this study. The incidences of pain and itching were low, 3% and 4% respectively. Many women with ear keloids expressed an inability to wear earrings because of the bulky lesions.

Inclusion Criteria: Because of the possibility of radiation to surrounding normal tissues and the remote chance of radiation induced cancer, most series have offered radiotherapy only to patients with recurrent keloids. These patients having been subjected to multiple surgeries, courses of

steroid injections and other therapies to no avail, are highly motivated to accept the risk of radiotherapy to obtain a cure.

In this study, 73% of patients have had their lesions surgically excised previously and 53% have tried steroid injections. Ledercort and Contratubex are the most common ointments tried. Recurrence with surgery alone has been reported to be 45 - 100%. In completely resolved cases, recurrence following steroid injections is anywhere between 9 - 50%.

Radiotherapy following surgery therefore has been recommended as the standard treatment of recurrent keloids.

This has been given in various ways.

External irradiation

Author	Recurrence (%)
Kovalic	27
Maarouf`	16
Sclafani	12.5
Raj Ragoowanshi	9
Berman	10
Chaudhry	2-8
Darzi	25

Linear Accelerator

Author	Recurrence (%)
Sallstrom	8
Mitsuhashi	16

Doornbos	10
Leibel & Phillips	2 - 27

Strontium 90 applicator

Author	Recurrence (%)
Fraunholz	36
Wagner	20

HDR Brachytherapy (Ir 192)

Author	Recurrence (%)
Garg	12
Guix	3.4

It has therefore been found that radiotherapy has been uniformly effective in bringing down the recurrence rate. The control was more

effective in patients with facial keloids (2%) than with thoracic keloids (49%). This result was statistically significant according to Wagner (p= 0.001).

The symptoms of keloid, like pain and itching were also considerably reduced i.e. p = 0.0005 *(Fraunholz)*. 60% of patients were satisfied with the cosmetic outcome.

Kal et al calculated biologic effective doses and stressed that a relatively high dose (preferably 30 GY) should be applied in an overall short treatment time (preferably within 2 days of surgery).

This is where HDR Brachytherapy scores over other modalities as high doses can be imparted locally within a short time.

In this study, the overall control rate has been 93.3% and compares favourably with literature.

The most common problem reported in the literature is hyper pigmentation, but authors have stressed that it is self limiting.

Guix	-	6.8%
Mitsuhashi	-	44%
Sallstrom	-	31%
This series	-	13%

There has not been a major adverse event or a proven case of secondary malignancy reported so far.

CONCLUSION

- Keloids are a vexing problem for patients and plastic surgeons.
- Once they occur, a single modality treatment is fraught with recurrence.
- Post excisional radiotherapy affords good control, but with the disadvantage of radiation to normal tissues.
- HDR Brachytherapy offers an ideal solution as -

  Can be done in an out patient basis

  Relatively low cost

  Excellent radiation protection

  Better dose distribution to tissues.

- With a local control rate of **93%** and no significant side effects, HDR Brachytherapy following surgery is an effective treatment of keloid scar.

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